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# Glomerulonephritis therapy: is there a role for green tea?

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**Rapidly progressive glomerulonephritis is the most aggressive form of glomerulonephritis with the worst prognosis. The current unspecific immunosuppressive therapy with corticosteroids and cytotoxic agents is often complicated by severe side effects. Peng and colleagues studied the therapeutic potential of the green tea component (−)-epigallocatechin-3-gallate (EGCG) in a murine model of immune-mediated glomerulonephritis. Their results indicate that EGCG treatment ameliorates renal inflammation, tissue damage, and loss of renal function and might therefore represent a novel therapeutic approach for human glomerulonephritis.**

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Glomerulonephritis as a disease category is one of the leading causes of end-stage renal disease in the Western world and is associated with increased morbidity and mortality. The most aggressive form of glomerulonephritis with the worst clinical outcome is rapidly progressive glomerulonephritis (RPGN).[1] RPGN represents a heterogeneous collection of disease entities that are characterized by immune-mediated renal damage, consisting of a specific immune reaction followed by an effector phase of inflammation. This pathophysiological concept is the current rationale for unspecific immunosuppressive therapy with corticosteroids and cytotoxic agents;[1] however, the missing specificity of these therapeutic regimes and frequently disabling side effects are the main reasons for the urgent need to develop new and more specific individual therapeutic strategies. In recent years, very few innovative induction therapies for RPGN have been established in clinical practice; these include mycophenolate mofetil for lupus nephritis[2] and, very recently, rituximab for ANCA-associated glomerulonephritis.[3]

Green tea has been considered a healthy beverage since the beginning of its history, used in traditional Chinese medicine as a treatment for various disease conditions, and to prolong life in general.[4] More recent investigations on green tea extracts, and more specifically the green tea component (−)-epigallocatechin-3-gallate (EGCG), have suggested that these compounds mediate protection from prostate and breast cancer, as well as cardiovascular disease.[5] However, *in vivo* evidence to support their beneficial effect in immune-mediated diseases is limited. In experimental models of multiple sclerosis[6] and Sjögren's syndrome,[7] application of EGCG has been shown to reduce the oxidative stress response and production of inflammatory mediators, resulting in amelioration of inflammation and improved outcome. With respect to renal disease, the indisputable ability of this compound to protect from oxidative stress has so far been applied only to models of kidney injury, such as cisplatin-induced nephrotoxicity[8] and diabetic nephropathy.[9]

Thus, the identification of new molecular targets that may be exploited for therapeutic intervention in crescentic glomerulonephritis is a priority in nephrology, with emphasis on minimizing the side effects associated with drug toxicity and immunosuppression. Most of the research in this field relies on animal models of crescentic glomerulonephritis, of which nephrotoxic nephritis (NTN) is by far the best characterized.[10] In mice, NTN is induced by injection of a heterologous antibody raised in sheep or rabbits that binds to the murine glomerular basement membrane; this induces a xenogenic immune response, resulting in immune-mediated glomerular damage, crescent formation, and tubulointerstitial leukocyte infiltration, a pathology that closely resembles human crescentic glomerulonephritis.[10]

Peng and colleagues[11] (this issue) now introduce the green tea component EGCG as a potential therapeutic compound for immune-mediated glomerulonephritis. Using the murine NTN model (here named murine anti-GBM glomerulonephritis), they show that oral administration of EGCG ameliorates the clinical course of the nephritis. Continuous treatment with EGCG, started 2 days before induction of NTN, substantially reduced crescent formation, proteinuria, and loss of renal function at day 15. This improved clinical outcome was accompanied by less glomerular and tubulointerstitial infiltration of macrophages and T cells. The authors convincingly demonstrate that EGCG therapy ameliorates the oxidative stress response that contributes to the development of immune-mediated kidney injury in nephritic mice. The increased levels of markers for oxidative stress detected in kidney tissue and urine of vehicle-treated animals with NTN were found to be normal in the EGCG-treated group. In further experiments, the authors analyzed various enzymes involved in the metabolism of reactive oxygen species (ROS). In the inflamed kidneys of mice with NTN, they found a pattern consistent with increased ROS generation along with a reduced capacity for ROS degradation. This deleterious shift in renal ROS metabolism was counteracted by EGCG therapy. In line with these data, other targets that are supposedly downstream of the oxidative response were also downregulated in the therapeutic group. Increased levels of

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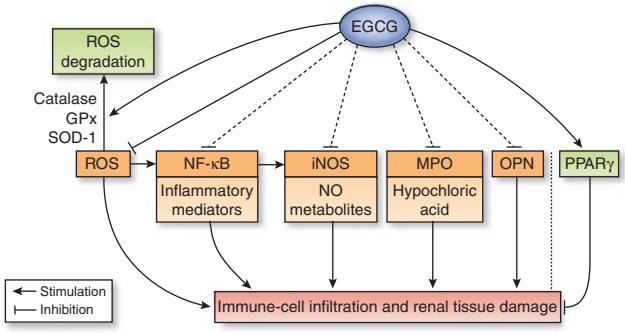


**Figure 1 | Proposed mechanisms for the anti-inflammatory effects of (−)-epigallocatechin-3-gallate in immune-mediated glomerulonephritis.** (−)-Epigallocatechin-3-gallate (EGCG) attenuates immune-mediated kidney injury by acting on multiple targets in the inflammatory cascade. Inhibiting the generation of reactive oxygen species (ROS) and facilitating their degradation are probably among the most important mechanisms. Furthermore, EGCG has been shown to upregulate renal expression of the anti-inflammatory transcription factor peroxisome proliferator-activated receptor γ (PPARγ). GPx, glutathione peroxidase; iNOS, inducible nitric oxide synthase; MPO, myeloperoxidase; NF-κB, nuclear factor-κB; NO, nitric oxide; OPN, osteopontin; SOD-1, superoxide dismutase 1.

myeloperoxidase and inducible nitric oxide synthase that generate highly cytotoxic hypochloric acid and nitric oxide metabolites, respectively, were reversed by EGCG. Furthermore, activity of the central inflammatory transcription factor nuclear factor-κB and the chemoattractant osteopontin was inhibited, providing a possible explanation for the reduced leukocyte recruitment to the kidney that is observed under EGCG therapy.

The mechanisms by which EGCG administration is presumed to mediate its anti-inflammatory effect in immune-mediated glomerulonephritis are summarized in Figure 1.

In a second set of experimental mice, the authors identify the anti-inflammatory transcription factor peroxisome proliferator-activated receptor γ (PPARγ) as another potential target of the pluripotent green tea compound. The PPARγ level, found to be markedly downregulated in the kidneys of vehicle-treated nephritic mice, was restored by EGCG treatment, suggesting that PPARγ activation might be crucial for its beneficial effects. To underline the importance of PPARγ for EGCG-mediated protection, the authors applied a PPARγ antagonist together with EGCG to mice with NTN. In line with the hypothesis, concomitant treatment almost completely abrogated the beneficial effects of the EGCG therapy in terms of kidney function and histopathological injury.

As in many therapeutic studies based on animal models, the data presented so far are hampered by differences in the disease course; whereas the mouse model requires a pretreatment episode prior to the induction of the disease, human autoimmune diseases develop chronically, and patients commonly have a long history of disease at the time of diagnosis. To provide further evidence for the potential benefits of EGCG as a therapeutic compound for human RPGN, the authors performed another set of experiments in which they initiated EGCG therapy after full-blown nephritis had developed. In these experiments they showed that treatment with EGCG from day 7 after induction of NTN to day 28 was also able to protect from renal tissue injury and loss of renal function. Perhaps most importantly, the delayed treatment reduced the lethality from more than 40% to 10%.

In summary, the study of Peng and colleagues[11] provides the first experimental evidence that green tea extracts are of therapeutic value in the treatment of a mouse model of RPGN, and hopefully in humans in the future. This treatment strategy could be particularly attractive as green tea extracts have been shown to modulate the inflammatory cascade by multiple mechanisms, and are believed to have a favorable safety profile.[12] However, future studies to evaluate therapeutic EGCG application in humans are needed to investigate whether this innovative approach can be translated to treatment of patients with glomerulonephritis in clinical practice.

## DISCLOSURE

The author declared no competing interests.


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